

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
WO 2004/064738 A3

(51) International Patent Classification⁷: **C07D 211/06**,
A61K 31/4468, A61P 25/14, 25/16, 25/18, 25/28, 25/24,
25/06

San Diego, CA 92130 (US). BRANN, Mark, R. [US/US];
2950 Racetrack View Drive, Del Mar, CA 92014 (US).

(21) International Application Number:
PCT/US2004/001234

(74) Agent: **HART, Daniel**; Knobbe, Martens Olson & Bear,
LLP, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US).

(22) International Filing Date: 15 January 2004 (15.01.2004)

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/441,406 16 January 2003 (16.01.2003) US
60/479,346 17 June 2003 (17.06.2003) US

(71) Applicant (for all designated States except US): **ACA-
DIA PHARMACEUTICALS INC.** [US/US]; 3911 Sor-
rento Valley Blvd., San Diego, CA 92121-1402 (US).

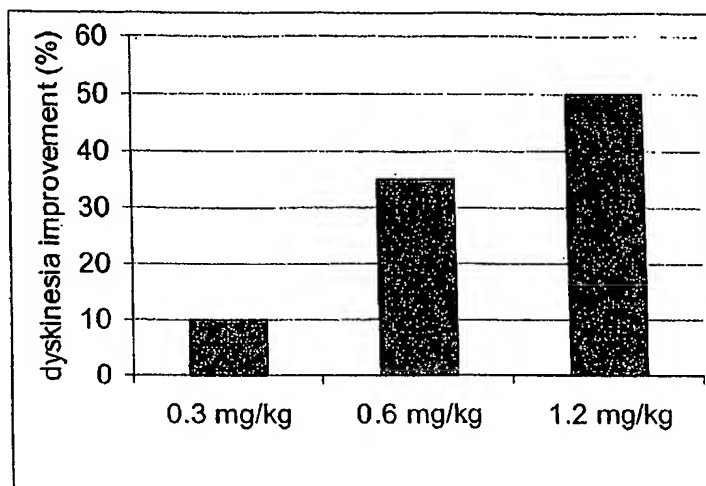
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,
GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **WEINER, David**,
M. [US/US]; 4915 Muir Avenue, San Diego, CA 92107
(US). **DAVIS, Robert, E.** [US/US]; 13272 Glencliff Way,

[Continued on next page]

(54) Title: SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGEN-
ERATIVE DISEASES



(57) Abstract: Behavioral pharmacological data with the compound of formula (I), a novel and selective 5HT_{2A/2C} receptor inverse agonist, demonstrate *in vivo* efficacy in models of psychosis and dyskinesias. This includes activity in reversing MK-801 induced locomotor behaviors, suggesting that this compound may be an efficacious anti-psychotic, and activity in an MPTP primate model of dyskinesias, suggesting efficacy as an anti-dyskinesia agent. These data support the hypothesis that 5HT_{2A/2C} receptor inverse agonism may confer antipsychotic and anti-dyskinetic efficacy in humans, and indicate a use of the compound of formula (I) and related agents as novel therapeutics for Parkinson's Disease, related human neurodegenerative diseases, and psychosis.



Published:

— with international search report

(88) Date of publication of the international search report:

25 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2004/001234

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D211/06 A61K31/4468 A61P25/14 A61P25/16 A61P25/18 A61P25/28 A61P25/24 A61P25/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K C07D A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 877 173 A (FARBER NURI B ET AL) 2 March 1999 (1999-03-02) claims 1,30	9-13
X	US 3 983 234 A (SAYERS ANTHONY CAMPBELL) 28 September 1976 (1976-09-28) column 1, line 1 - line 17	9-13, 17-20
X	FRIEDMAN J H: "Clozapine treatment of psychosis in patients with tardive dyskinesia: report of three cases" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 9, no. 3, 1 May 1994 (1994-05-01), pages 321-324, XP009032726 page 321, right-hand column, paragraph 3 page 323, right-hand column, paragraph 3 <div style="text-align: center;">-/--</div>	25-28
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center;">14 July 2004</div>		Date of mailing of the international search report <div style="text-align: center;">08/09/2004</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Albayrak, T</div>

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US2004/001234

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YOSHIDA K ET AL: "Marked improvement of tardive dystonia after repoacing haloperidol with risperidone in a schizophrenic patient" CLINICAL NEUROPHARMACOLOGY, vol. 21, no. 1, 1998, pages 68-69, XP009032725 page 69, left-hand column - right-hand column	25-28
X	----- DELECLUSE F ET AL: "A case of tardive tremor successfully treated with clozapine" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 13, no. 5, September 1998 (1998-09), pages 846-847, XP009032724 the whole document	25-28
X	----- FACTOR S A ET AL: "Clozapine prevents recurrence of psychosis in Parkinson's disease" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 7, no. 2, 1992, pages 125-131, XP009032679 page 130, right-hand column, paragraph 2	32-35, 39
X	----- FACTOR ET AL: "Clozapine for the treatment of drug-induced psychosis in Parkinson's disease: results of the 12 week open label extension in the PSYCLOPS trial" MOVEMENT DISORDERS OFFICIAL JOURNAL OF THE MOVEMENT DISORDER SOCIETY, vol. 16, no. 1, January 2001 (2001-01), pages 135-139, XP009032680 page 138, right-hand column, paragraph 2	32-35, 39
X	----- US 2002/165225 A1 (KANKAN RAJENDRA N ET AL) 7 November 2002 (2002-11-07) page 1, right-hand column, paragraph 8 - page 2, left-hand column, paragraph 1 claims 12,16	32-35, 39-44, 46
X	----- US 6 358 698 B1 (BRANN MARK R ET AL) 19 March 2002 (2002-03-19) claims 9,10 column 1, paragraph 1 column 4, line 60 - line 64 column 5, line 59 - column 6, line 14 tables 2,3 ----- -/--	32-35, 39-44, 46

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/001234

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HERRICK-DAVIS ET AL: "Inverse Agonist Activity of Atypical Antipsychotic Drugs at Human 5-Hydroxytryptamine_{2C} Receptors" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 295, no. 1, October 2000 (2000-10), pages 226-295, XP001182089 figures 1-3 table 1</p> <p>-----</p>	1-86

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/001234

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5877173	A	02-03-1999	NONE	
US 3983234	A	28-09-1976	NONE	
US 2002165225	A1	07-11-2002	US 6348458 B1	19-02-2002
			AT 6739 U1	25-03-2004
			AU 2017601 A	09-07-2001
			CA 2395774 A1	05-07-2001
			DE 20023184 U1	03-04-2003
			DK 200300161 U1	16-06-2003
			DK 200300221 U1	25-08-2003
			DK 200300222 U1	25-08-2003
			EP 1246827 A1	09-10-2002
			WO 0147933 A1	05-07-2001
			NZ 519926 A	27-02-2004
			ZA 200205228 A	30-06-2003
			IN 187439 A1	27-04-2002
US 6358698	B1	19-03-2002	AU 6391299 A	26-04-2000
			WO 0020636 A1	13-04-2000